REMARKS

STATUS OF THE CLAIMS

Claims 1, 2, 4, 5, 7, 8, 10, 11, 13-15, 21-26, 31, 34, 35 and 38-49 were pending. Claims 1, 2, 4, 5, 7, 8, 10, 11, 13-15, 21-26, 31, 35 and 38-47 have been withdrawn from consideration and claims 34, 48 and 49 were under consideration.

Claim 34 has been amended to clarify that the switching system is a complex (*see,* page 10, lines 16-19) comprising a heterodimer (page 2, lines 8-11) of first and second polypeptides (that bind to DNA) and a ligand.[1] In addition, claim 34 also indicates that the first or second polypeptide is an engineered Cys2-His2 zinc finger protein (*see*, for example, page 23, line 4 through page 31, line 31). Claim 48 has been amended to indicate that one of the polypeptide components of the switching system comprises a Cys2-His2 zinc finger. Claim 49 has been canceled, without prejudice or disclaimer.

Withdrawn method claims 1, 2, 7, 8, 21, 22, 24, 35, 38, 39, 40 and 46 have been amended to incorporate all the limitations of pending composition claim 34. Thus, rejoinder of all method claims is in order upon indication that claim 34 is allowable.

Accordingly, claims 1, 2, 4, 5, 7, 8, 10, 11, 13-15, 21-26, 31, 34, 35 and 38-48 are pending as shown above and claims 34 and 48 are under consideration.

INTERVIEW SUMMARY

Applicants note with appreciation the telephone interview conducted on August 4, 2006, in which Examiner Sullivan, Sean Brennan and the undersigned participated. Alternative claim language discussed during this interview has been incorporated, as shown above.

35 U.S.C. § 101

Applicants acknowledge withdrawal of the previous rejection of claim 34 under this section. Office Action at page 2.

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[1] Applicants note that the Office has previously acknowledged that binding of the ligand to both polypeptide components of the complex is fully disclosed in the specification. *See* Office Action dated November 15, 2005 at page 2-3.

Examined claim 49 was rejected under 35 U.S.C. § 101 as allegedly directed to non-statutory subject matter for containing the term "mutant." *See* page 3 of the Office Action.

Claim 49 has been canceled by amendment herein, thereby obviating this rejection.

With regard to claims 34 and 48, it was agreed during the interview that indication that the zinc finger proteins were engineered would be sufficient to indicate the "hand of the inventor" and to address the Examiner's concern that "non-naturally occurring" is not sufficiently clear.

35 U.S.C. § 112, 2nd Paragraph

Claim 34 was rejected as allegedly indefinite for reciting "non-naturally occurring." (Office Action, pages 4-5).

For the reasons discussed during the August 4, 2006 interview, Applicants submit that the term "non-naturally occurring" is not indefinite inasmuch as the skilled artisan is fully apprised of the metes and bounds of the claims – any later discovered naturally occurring zinc finger proteins would not be encompassed. In any event, the term "non-naturally occurring" has been removed from claim 34, thereby obviating the rejection.

Claim 49 was rejected as allegedly indefinite for reciting mutant proteins. (Office Action, page 5). Inasmuch as claim 49 has been cancelled, the rejection is moot.

35 U.S.C. § 102

Applicants acknowledge withdrawal of the previous rejection of claim 34 under this section. (Office Action at page 3).

The following new rejections were made.

(A) Claim 49 was rejected as allegedly anticipated by any of: (1) Porter *et al* as evidenced by Pratt *et al.*, (2) Kobayashi *et al.*, or (3) Perkins *et al.*, in light of Prosite Database entry PDOC00028. (Office Action, pages 6-9).

In light of the cancellation of claim 49, these rejections are moot.

(B) Claims 48 and 49 were rejected as allegedly anticipated by Liden *et al.* as evidenced by McEwan *et al.* and Bledsoe *et al.* In support of the rejection, The Office states that Liden discloses various mutants of the glucocorticoid receptor (GR), McEwan discloses the DNA-binding domain of the glucocorticoid receptor and the binding of GR to DNA as a homodimer, and Bledsoe discloses that hormone binding allows dimerization of GR and translocation into the nucleus. Office Action, pp. 10-11.

With respect to claim 48, Applicants note that this claim recites a Cys2-His2 zinc finger binding domain. Because the glucocorticoid receptor disclosed by Liden *et al.* does not contain a Cys2-His2 zinc finger binding domain,[2] Liden *et al.* fail to disclose the claimed subject matter.[3]

With respect to claim 49, the rejection is moot in light of the cancellation of this claim.

35 U.S.C. § 103

Claims 34, 48 and 49 were rejected as allegedly obvious over Vegeto, WO 93/23431 (as evidenced by McEwan *et al.* and Bledsoe *et al.*) in light of Liu *et al.* (Office Action, pages 12-14). In support of the rejection, the Office Action states that Vegeto discloses mutated steroid hormone receptors and their uses as a molecular switch for regulating nucleic acid expression in mammals, and glucocorticoid receptors as starting material for making such mutant receptors. The Office concludes that, in light of McEwan's disclosure of the DNA-binding domain of the glucocorticoid receptor and the binding of GR to DNA as a homodimer (Office Action, page 10), and Bledsoe's disclosure that hormone binding allows dimerization of GR and translocation into the nucleus (Office Action, page 10), Vegeto discloses a switching system comprising two polypeptides and a ligand.

The Office notes that although Vegeto, in light of McEwan and Bledsoe, fails to disclose a switching system in which one of the polypeptides comprises a non-naturally-

[2] The GR receptor is a Cys4 protein. See, for example, Liden *et al.* at page 21467, second column, lines 1-3; and McEwan *et al.* at Figure 1

[3] These considerations also apply to pending claim 34

occurring Cys2-His2 zinc finger, or an engineered or mutated zinc finger binding domain; Vegeto teaches that the DNA binding domain of a modified steroid receptor can be replaced. Based on this statement, the Office asserts that it would have been obvious to combine Vegeto's disclosure with that of Liu, who teaches design and construction of selective six-finger zinc finger proteins. Motivation for this combination is said to derive from the nature of the problem to be solved by Vegeto; *i.e.*, regulation of expression of a nucleic acid in mammals, and Liu's capability of designing a protein that will bind to a single site in a mammalian genome. *Id.*

In response, Applicants disagree that the problem solved by Vegeto's disclosure required the ability to uniquely address a single site in a mammalian genome. Vegeto discloses modified steroid receptors and the use of these modified receptors to determine hormone agonists and antagonists (*e.g.*, page 5, lines 21-25; page 6, lines 1-7), to identify ligands (*e.g.*, page 6, lines 8-16) and to obtain modified receptors that were regulated by non-natural ligands for use as a molecular switch in gene therapy (*e.g.*, page 7, lines 20-27; page 17, lines 1-30). With respect to the use of her invention for regulation of gene expression, Vegeto makes clear that her modified steroid receptors are used in conjunction with heterologous sequences. For example, Vegeto uses the term "nucleic acid cassette" in the sections of her application related to the use of modified steroid receptors in gene regulation (*e.g.*, page 7, lines 20-27; page 17, lines 1-30). Vegeto defines "nucleic acid cassette" as genetic material that is incorporated into a cell and oriented in a vector (page 10, line 30 through page 11, line 4).

Thus, all of Vegeto's disclosure relating to the use of modified steroid receptors for regulation of gene expression is directed to regulation of exogenous genes and accordinglydoes not require the ability to address a single site in a mammalian genome. All that Vegeto requires is the ability to recognize the transcriptional element present in the vector in which the cassette is incorporated. Accordingly, there would not have been a motivation for one of skill in the art to combine the disclosures of Vegeto and Liu.

Moreover, assuming for the sake of argument that motivation for the combination of Vegeto and Liu had existed, the hypothetical modification of Vegeto's mutant receptor by replacing its DNA-binding domain with Liu's zinc finger protein would generate a

non-functional product. A fusion protein comprising a six-finger zinc finger binding domain (recognizing an 18-nucleotide target site) joined to a steroid receptor would have to bind to a 36-nucleotide sequence (consisting of a repeat of the 18-nucleotide target) in order to function as a dimer. The chance of such a specific sequence occurring in a mammalian genome is 1 in 4^{36} or approximately 5×10^{-21}. Alternatively, binding of a single steroid receptor/zinc finger fusion protein to an 18-nucleotide site would not function to regulate gene expresssion, since steroid receptors function as homodimers. Thus, the proposed modification of Vegeto's invention would render it non-functional.

Finally, Applicants note that claim 34 recites a heterodimeric complex, as opposed to the monomer or homodimer that would result from the combination of Vegeto and Liu.

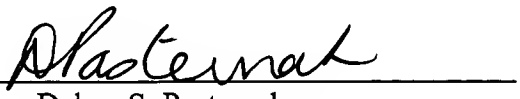
For all of the aforementioned reasons, Applicants submit that the Office has failed to make a *prima facie* case of obviousness and, therefore, the rejection should be withdrawn.

CONCLUSION

Applicants submit that the claims are in condition for allowance and request early notification to that effect. If the Examiner has any further issues or wishes to discuss any of the foregoing, he is invited to contact Applicants' undersigned attorney at the telephone number listed below.

Respectfully submitted,

Date: August 9, 2006

By: 

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